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10/840,182

05/05/2004

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EXAMINER

PANDE, SUCHIRA

ART UNIT	PAPER NUMBER
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1637

MAIL DATE	DELIVERY MODE
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05/09/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/840,182	Applicant(s) CLEARY ET AL.	
	Examiner Suchira Pande	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 January 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7,10,11,13,18,19,23,28,31 and 33-37 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7,10,11,13,18,19,23,28,31 and 33-37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 23 January 2007 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Amendment

1. This office action is in response to an amendment filed on January 23, 2007. Claims 1-41 were previously pending. Applicant amended claims 1 and 5; cancelled claims 38-41; and withdrew claims 8-9, 12, 14-17, 20-22, 24-27, 29-30 and 32. Claims 1-7, 10-11, 13, 18-19, 23, 28, 31 and 33-37 are currently pending and will be examined.

Petition for Acceptance of Color Drawings

2. Applicant has submitted color drawings thereby overcoming the objection to the Drawings. See MPEP section 6.23.01. The petition filed on January 23, 2007 explaining why the color drawings are necessary is granted.

Specification

3. Applicant's amendments to Specification overcome the issues related to use of trademark.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Regarding claim 1 (Currently Amended) Veres and Stadtman (1994) Proc. Natl. Acad. Sci. USA vol. 91, pp. 8092-8096 teach a method of biosynthetically labeling RNA

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in a cell of interest (see page 8092 abstract where bulk thio-tRNA preparation from *E. coli* and *S. typhimurium* are taught) the method comprising : contacting said cell with a purine or pyrimidine analog having a reactive moiety not normally present in RNA, wherein said cell comprises a phosphoribosyltransferase or nucleoside kinase or phosphorylase that can specifically incorporate said purine or pyrimidine analog into the corresponding nucleotide (Since 2-thiouridine is not normally a component of RNA therefore it is inherently obvious that the strain of *E. coli* that can produce the thiolated tRNA contains the enzymes necessary to convert the purine or pyrimidine analogs into RNA containing 2-thiouridine. The *E.coli asuE* mutant strain is unable to synthesize 2-thiouridines (see page 8092 par. 2 where such strain is described. This is presumably because the strain lacks the enzymes necessary to convert the purine or pyrimidine analogs into RNA containing 2-thiouridine) and wherein said purine or pyrimidine analog is incorporated into RNA comprising said reactive moiety synthesized by said cell (see page 8094 last paragraph, where bulk thio-tRNA preparation from *E. coli* and *S. typhimurium* are taught. Hence Veres and Stadtman inherently teach incorporation of purine or pyrimidine analog into RNA comprising said reactive moiety synthesized by said cell (thio uridine in this case); obtaining RNA comprising said reactive moiety from said cell (see where bulk preparation of thio-tRNA is taught); and conjugating a tag to said reactive moiety (see page 8094 Table 5 where labeling of tRNA containing 2-thiouridine with ⁷⁵Se is taught. This labeling is achieved by conjugating the ⁷⁵Se tag to the reactive thiol moiety of 2-thiouridine is explicitly stated on page 8095 par. 3 where Veres and Stadtman state "a direct attack of selenophosphate on carbon-2 of the

thiouridine residue results in the addition of selenium and concomitant elimination of sulfur."

Thus all elements of amended claim 1 are anticipated by Veres and Stadtman.

Regarding claim 33, Veres and Stadtman teach a method of biosynthetically labeling RNA in a cell of interest, the method comprising: contacting said cell with a uracil analog having a reactive thiol moiety not normally present in RNA, wherein said cell comprises a uracil phosphoribosyltransferase (UPRT) that can convert said uracil analog to the corresponding uridine monophosphate; wherein said uridine analog is incorporated into RNA synthesized by said cell. (since Veres and Stadtman teach synthesis of t-RNA containing 2-thiouridine (thio-moiety is not normally present in cells) from cells of E. coli see above. Therefore they inherently teach that these E.coli cells must contain the necessary uracil phosphoribosyltransferase to convert uracil analog to the corresponding uridine monophosphate; wherein said uridine analog is incorporated into RNA synthesized by said cell.

Response to arguments re 103 rejection

5. Regarding rejections using Trudeau et al. Applicant provides arguments that thio analogs (thioguanine and 6-Thioguanine) taught by Trudeau when incorporated into RNA do not retain the reactive moiety not normally present in the cell. This argument is considered valid by Examiner accordingly in this Office Action, Veres and Stadtman is being cited to teach incorporation of 2-thiouridine that contains a thiol moiety that is not normally present in RNA which is incorporated into RNA. They further teach isolation of

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this 2- thiouridine containing RNA and use the thio group as a reactive moiety to which a small molecule ^{75}Se as a tag is conjugated.

6. Regarding rejections using Al-Anouti et al. Applicant provides arguments why the uracil analog taught by Al- Anouti will not be useful for labeling RNA. These arguments are scientifically sound. In the present Office action teachings of Al- Anouti et al. are being used to provide indication that one of ordinary skill in the art knows that UPRT enzyme from *T. gondii* is capable of performing all the necessary steps required to convert a uracil analog fed to bacterial cells into nucleotides that get incorporated into RNA synthesized by cell. Explicitly Veres and Stadtman teach that thiolated RNA can be obtained from *E. coli* cells. Al-Anouti et al. explicitly describes UPRT enzyme from *T. gondii* that is capable of converting uracil analogs to corresponding mononucleotide that can be incorporated into RNA.

7. Regarding rejections using Iltzsch and Tankersley, the statement " several selected compounds were evaluated as substrates for *T.gondii* UPRTase, and it was found that in addition to emimycin and 5-fluorouracil, 2,4-dithiouracil is also a substrate for this enzyme" (see page 781, last 4 lines of Iltzsch and Tankersley). This clear teaching indicates to one of ordinary skill that 2,4-dithiouracil is a substrate for UPRTase therefore if 2,4-dithiouracil is used to feed the bacterial cells containing UPRTase then it will be converted to its corresponding mononucleotide that will get incorporated into RNA and the resulting RNA will contain thio residue. The thio containing RNA can be isolated in bulk is taught by Veres and Stadtman, hence now

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one of ordinary skill is in possession of thiolated RNA that can be conjugated with desired labeling residue using the thiol reactive group chemistry.

Claim Rejections - 35 USC § 103

8. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

9. Claims 1-7, 10-11, 13, 18-19, 23-28 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Veres and Stadtman (1994) Proc. Natl. Acad. Sci. USA vol. 91, pp. 8092-8096 as applied to claim 1 above in view of Trudeau et al. (2001) Human Gene Therapy 12:1673-1680; and further in view of Rana P.G. Pub 2004/0175732 filed on November 17, 2003 with a priority date of November 15, 2002.

Regarding claim 1, (Currently Amended) Veres and Stadtman (1994) Proc. Natl. Acad. Sci. USA vol. 91, pp. 8092-8096 teach A method of biosynthetically labeling RNA in a cell of interest, the method comprising : contacting said cell with a purine or pyrimidine analog having a reactive moiety not normally present in RNA, wherein said cell comprises a phosphoribosyltransferase or nucleoside kinase or phosphorylase that can specifically incorporate said purine or pyrimidine analog into the corresponding nucleotide, and wherein said purine or pyrimidine analog is incorporated into RNA comprising said reactive moiety synthesized by said cell ;obtaining RNA comprising said reactive moiety from said cell; and conjugating a tag to said reactive moiety (see above).

Regarding claim 4, Veres and Stadtman teach wherein said reactive moiety is at least one thiol group (see claim 1 above where 2-thiouridine containing at least one thiol group is taught).

Regarding claim 5, Veres and Stadtman teach a method of biosynthetically labeling RNA in a cell of interest, the method comprising: contacting said cell with a uracil analog having a thiol moiety not normally present in RNA and that can specifically incorporate said uracil analog into the corresponding nucleotide, and wherein said uracil analog is incorporated into RNA comprising said thiol moiety; obtaining RNA comprising said thiol moiety from said cell; and conjugating a small molecule binding partner to said thiol moiety (see above as applied to claim 1 above).

Regarding claim 5, Veres and Stadtman do not teach, wherein said cell comprises a phosphoribosyltransferase or nucleoside kinase operably linked to a promoter that can be activated in said cell.

Regarding claim 2, Veres and Stadtman teach method of claim 1, but do not teach *wherein sequences encoding said phosphoribosyltransferase or nucleoside kinase are operably linked to a promoter that is active or can be activated in said cell*

Regarding claims 2 and 4, Trudeau et al. teaches *wherein sequences encoding said phosphoribosyltransferase or nucleoside kinase are operably linked to a promoter that is active or can be activated in said cell*. (see page 1674 par. 3 where construction of pTbiGFP construct by inserting HGPRT gene into the multiple cloning site of AP2, a retroviral vector expressing enhanced green fluorescent protein (EGFP) is taught. Here

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sequence encoding HGPRT gene is operably linked to a promoter that drives the expression of EGFP in this retroviral vector.)

Regarding claim 3, Trudeau et. al. teaches *wherein said sequences encoding said phosphoribosyltransferase or nucleoside kinase are exogenous to the cell of interest.* (see page 1675 par. 4 where Trudeau et. al. teaches uptake of allopurinol by stably transduced cell lines A549, H322 and DA3. Here HGPRT sequences are exogenous (derived from *Trypanosoma brucei*) to the cells (A549, H322 and DA3) of interest.

Regarding claim 23, Trudeau et al. teaches *wherein said promoter is constitutively active in said cell of interest.* (see page 1676 Fig. 1 and Fig. Legend for Fig. 1 A, where plasmid pTbiGFP expresses HGPRT gene under control of a constitutively active CMV, cytomegalovirus promoter element. Thus Trudeau et. al. teaches wherein said promoter is constitutively active in said cell of interest).

Regarding claim 28, Trudeau et al. teaches *wherein said sequences encoding said phosphoribosyltransferase or nucleoside kinase are introduced into said cell of interest on a replicable vector.* (see page 1674 par. 6 where E.coli cells containing TbHGPRT gene was overexpressed, here TbHGPRT is a cDNA clone provided by B. Ullman. This TbHGPRT cDNA clone is obviously present on a replicable vector that has an inducible promoter capable of expression in *E.coli* cell. Thus Trudeau et al. teaches wherein said sequences encoding said phosphoribosyltransferase are introduced into said cell of interest on a replicable vector.

Regarding claim 31, Trudeau et al. teaches *wherein said purine or pyrimidine analog is provided in the form of a nitrogenous base*. (see page 1676 par. 4 where purine analog allopurinol an isomer of hypoxanthine a natural base is taught. Thus Trudeau et al. teaches wherein said purine or pyrimidine analog is provided in the form of a nitrogenous base (allopurinol).

C) Regarding claim 1, Rana teaches: *conjugating a tag to said reactive moiety*. (see page 1 par. 0004 where Rana teaches addition of tags such as biotin, psoralen-biotin and 4-thiobiotin to isolated RNA. See Fig. 8 D and page 6, par. 0065 where Rana teaches biotinylated RNA molecule labeled with 4-thio uridine or 6-thioguanosine. Binding to streptavidin coated beads selectively enriches RNA isolated from cell for RNA molecules containing biotin tag.

Regarding claim 6, Rana teaches *wherein said tag is a small molecule binding partner*. (see page 1, par. 0004 where small molecule binding partner biotin is taught as a tag)

Regarding claim 7, Rana teaches *wherein said tag is biotin*. (see page 1, par. 0004 where small molecule binding partner biotin is taught as a tag)

Regarding claim 10, Rana teaches *method further comprising the step of binding a specific binding partner to said tag*. (see page 6, par. 0065 where the step of binding streptavidin, a specific binding partner to said tag biotin is taught).

Regarding claim 11, Rana teaches *wherein said specific binding partner is conjugated to an insoluble substrate for affinity chromatography, and wherein said biosynthetically labeled RNA is separated from non-labeled RNA*. (see page 6, par.

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0065 where use of streptavidin coated beads to separate biotin labeled RNA from total RNA is taught. Here specific binding partner (streptavidin) is conjugated to an insoluble substrate (beads) for affinity chromatography, and wherein said biosynthetically labeled RNA is separated from non-labeled RNA.

Regarding claim 13, Rana teaches *wherein said separated RNA is amplified*. (see page 6, par. 0069 where amplification of RNA by reverse transcription is taught).

Regarding claim 18, Rana teaches *wherein said specific binding partner is conjugated to a detectable label*. (see page 13, par. 0145 where avidin and streptavidin conjugated to different detectable labels magnetic particles, superparamagnetic microspheres are taught. Further Rana teaches custom synthesis of beads when biotin/avidin or biotin/streptavidin system is used. Thereby Rana teaches the specific binding partner could be labeled with any other desired detectable label)

Regarding claim 19, Rana teaches *wherein said detectable label is a fluorochrome, radiolabel, heavy metal label, or enzyme conjugate*. (see page 13, par. 0141 where detectable labels such as fluorochrome such as fluorescein, radiolabel such as ^{32}P etc are taught)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Trudeau et al. and Rana in the method of labeling RNA taught by Veres and Stadtman. The motivation to do so is provided by Trudeau et al. who teach the entire method and explain the principle in detail how parasite encoded phosphoribosyltransferase enzyme can be used to incorporate purine analogs into newly synthesized RNA but does not actually

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enunciate the method how this thio labeled RNA can be isolated from the cell. Veres and Stadtman provide the details how thio labeled RNA can be obtained from cells and used for further labeling in vitro. To one of ordinary skill in the art it would be evident that there was reasonable expectation of success that they would be able to isolate thiolated RNA and conjugate label to this thio moiety of isolated RNA by practicing the method of Veres and Stadtman in the cells that had been labeled using the method of Trudeau et al.

The motivation to combine the method of Rana in the method of Veres and Stadtman and Trudeau et al. is provided by Rana. Rana teaches conjugating a tag such as biotin to the thiolated RNA. The conjugation to biotin for example now allows one of ordinary skill in the art to exploit the biotin/streptavidin chemistry to isolate thiolated labeled RNA very efficiently.

10. Claims 33-35 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Veres and Stadtman (1994) Proc. Natl. Acad. Sci. USA vol. 91, pp. 8092-8096, in view of Al-Anouti et al. (January 2003) Biochemical and Biophysical Research Communications vol. 302: pp. 316-323.

Regarding claim 33, Veres and Stadtman teach synthesis of t-RNA containing 2-thiouridine (thio-moiety is not normally present in cells) from cells of E. coli see above. Thereby teaching incorporation of thiol containing uridine analog into RNA. Therefore they inherently teach that these E.coli cells must contain the necessary uracil phosphoribosyltransferase to convert uracil analog to the corresponding uridine

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monophosphate; wherein said uridine analog is incorporated into RNA synthesized by said cell. However they do not explicitly spell out how these enzymes might function.

A) Regarding claim 33, Al-Anouti et al. teach: *A method of biosynthetically labeling RNA in a cell of interest, the method comprising:*

contacting said cell with a uracil analog (see page 316 par. 1 where contacting the cells with uracil analog 5-fluoro-2'-deoxyuridine (FUDR) is taught)

having a reactive thiol moiety not normally present in RNA,

wherein said cell comprises a uracil phosphoribosyltransferase (UPRT) that can convert said uracil analog to the corresponding uridine monophosphate; (see page 316 par. 1 where a uracil phosphoribosyltransferase (UPRT) from Toxoplasma gondii (T. gondii) that can convert said uracil analog to the corresponding uridine monophosphate 5-fluorodeoxyuridine monophosphate is taught); Thereby Al-Anouti et al. teach how (UPRT converts said uracil analog to the corresponding uridine monophosphate)

Regarding claim 34, Al-Anouti et al. teaches *wherein sequences encoding said UPRT are operably linked to a promoter that is active or can be activated in said cell.* (see page 317 par. 4 where no of plasmids encoding UPRT under control of modified promoter of *T. gondii* surface antigen 1(SAG1) and their derivatives are taught. The plasmids containing UPRT gene under control of *T.gondii* promoter and pUC19UPRT plasmids all contain UPRT operably linked to a promoter that is active or can be activated in appropriate Human Foreskin Fibroblasts or *E.coli* cells respectively.)

Regarding claim 35, Al-Anouti et al. teaches *wherein said sequences encoding said UPRT are exogenous to the cell of interest.* (see page 317, par. 4 where

pUC19UPRT plasmid is taught.. These pUC based plasmids can be propagated in *E.coli*. Thus Al-Anouti et. al. teaches UPRT gene from *T.gondii* is exogenous to the cell of interest.)

Regarding claim 37, Al-Anouti et al. teaches *wherein said UPRT is Toxoplasma gondii UPRT or a functional derivative thereof*. (see page 316 title and abstract where *Toxoplasma gondii* uracil phosphoribosyltransferase (TgUPRT) is taught).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Al-Anouti et al. in the method of Veres and Stadtman.

Veres and Stadtman teach incorporation of thiol group into RNA, isolation of thiolated RNA in bulk from two different bacterial species (see above) and use this thiol group to conjugate small molecule radioactive selenium to this isolated RNA in vitro. They do not provide explanation as to how this labeling occurs and the enzymes involved. Al-Anouti et al. teach the entire method and explain the principle in detail how parasite encoded UPRT enzyme can be used to incorporate uridine analogs into newly synthesized RNA.

Thus by combining the two methods one of ordinary skill in the art has reasonable expectation of success in being able to thiolate newly synthesized RNA from cells containing UPRT enzyme.

11. Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Veres and Stadtman (1994) Proc. Natl. Acad. Sci. USA vol. 91, pp. 8092-8096, in view of Al-Anouti et al. (January 2003) Biochemical and Biophysical Research Communications

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vol. 302: pp. 316-323 as applied to claims 33-35 and 37 above further in view of Iltzsch and Tankersley (1994) Biochem Pharm. Vol. 48 (4): 781-792 cited by applicant in IDS.

Regarding claim 36, Veres and Stadtman & Al-Anouti et al. teaches the method of claim 33 but do not teach uracil analog 2,4 dithiouracil.

Regarding claim 36, Iltzsch and Tankersley teach uracil analog 2,4 dithiouracil. (see page 781 abstract where 2,4-dithiouracil a uracil analog containing thiol moiety not normally present in cell is taught as a substrate for *T. gondii* enzyme UPRT).

It would have been obvious to one of ordinary skill in the art to use uracil analog 2,4 dithiouracil taught by Iltzsch and Tankersley as a substrate to feed the bacterial cells in the method of Veres and Stadtman & Al-Anouti et al. The motivation to do so is provided by Iltzsch and Tankersley who teach 2,4-dithiouracil a uracil analog containing thiol moiety not normally present in cell is taught as a substrate for *T. gondii* enzyme UPRT. So the 2,4 dithiouracil could be incorporated into RNA using the UPRT enzyme present in the bacterial cell and thiolated RNA can be isolated from such a cell which in turn can be used to conjugate with desired label using the available thiol group in the RNA as a reactive moiety.

The statement " several selected compounds were evaluated as substrates for *T.gondii* UPRTase, and it was found that in addition to emimycin and 5-fluorouracil, 2,4-dithiouracil is also a substrate for this enzyme" (see page 781, last 4 lines of Iltzsch and Tankersley). This clear teaching indicates to one of ordinary skill that 2,4-dithiouracil is a substrate for UPRTase therefore if 2,4-dithiouracil is used to feed the bacterial cells containing UPRTase then it will be converted to its corresponding mononucleotide that

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will get incorporated into RNA and the resulting RNA will contain thio residue. The thio containing RNA can be isolated in bulk is taught by Veres and Stadtman, hence now one of ordinary skill is in possession of thiolated RNA that can be conjugated with desired labeling residue using the thiol reactive group chemistry. Thus use of 2,4-dithiouracil would obviate trial and error required to find out which of the possible thio containing uracil precursors would be efficiently used by UPRTase of *T. gondii*.

Conclusion

12. All claims under consideration 1-7, 10-11, 13, 18-19, 23, 28, 31 and 33-37 are rejected over prior art.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.


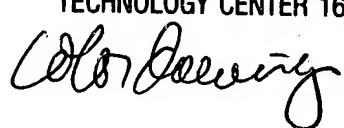
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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suchira Pande whose telephone number is 571-272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Suchira Pande
Examiner
Art Unit 1637


GARY BENZION, PH.D.
SUPERVISORY PATENT EXAMINER
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JEFFREY FREDMAN
PRIMARY EXAMINER
5/4/08